CLAIMS

1. A method of treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and which cells are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molecule, the method comprising administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL) which recognise at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell characterised in that the cytotoxic T lymphocytes ~~are not derived from the patient with a disease.~~ < >

2. A method according to Claim 1 wherein the CTL are a clonal population of CTL.

3. A method according to Claim 1 or 2 wherein the CTL are substantially free of other cell types.

4. A method according to any one of Claims 1 to 3 wherein said molecule is a polypeptide.

~~5. A method according to any one of Claims 1 to 4 wherein the CTL are derived from an individual other than the patient.~~

~~6. A method according to any one of Claims 1 to 5 wherein the CTL~~ < are derived from an individual which individual does not carry the HLA class I (or equivalent) molecule type which, in the patient, presents at least part of said abnormal molecule, or molecule

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abnormally elevated, contained in or associated with the diseased cells of said patient.

5 7. A method according to Claim 4 wherein said polypeptide is a mutant polypeptide associated with said diseased cells.

6 8. A method according to Claim 4 wherein said polypeptide is present at a higher level in said diseased cells compared to non-diseased cells.

7 9. A method according to any one of the preceding claims wherein the disease is a cancer.

8 10. A method according to Claim 7 wherein the cancer is ~~any one of~~ any one of breast cancer; bladder cancer; lung cancer; prostate cancer; thyroid cancer; leukaemias and lymphomas such as CML, ALL, AML, PML; colon cancer; glioma; seminoma; liver cancer; pancreatic cancer; bladder cancer; renal cancer; cervical cancer; testicular cancer; head and neck cancer; ovarian cancer; neuroblastoma and melanoma.

9 11. A method according to any one of Claims 1 to 6 wherein the disease is caused by a chronic viral infection.

10 12. A method according to Claim 9 wherein the virus is any one of HIV, papilloma virus, Epstein-Barr virus, HTLV-1, hepatitis B virus, hepatitis C virus and herpes virus.

11 13. A method according to Claim 10 wherein the virus is HIV.

12 ~~14~~. A method according to any one of Claims 1 to ~~8~~ 6 wherein the disease is associated with an abnormally elevated amount of a hormone.

5 13 ~~15~~. A method according to any one of Claims 1 to ~~8~~ 6 wherein the disease is a bacterial disease caused by a chronic bacterial infection.

14 ~~16~~. A method according to any one of the preceding claims further 10 comprising the step of determining the HLA class I (or equivalent) molecule type of the patient prior to administration of the CTL.

15 ~~17~~. A method according to Claim ~~16~~ 14 wherein the said type is determined using DNA typing.

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16 ~~18~~. A method according to any one of the preceding claims wherein the patient is human.

17 ~~19~~. A method according to Claim ~~16~~ 14 ~~when dependent on Claim 6~~ 20 wherein said cytotoxic T lymphocyte is selected from a library of CTL clones, said library comprising a plurality of CTL clones derived from individuals with differing HLA class I (or equivalent) molecule type and each said CTL clone recognises said diseased cells.

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18 ~~20~~. A method according to Claim ~~19~~ 17 wherein each said CTL clone recognises at least part of the same molecule contained in or associated with said diseased cells.

30 19 ~~21~~. Use of cytotoxic T lymphocytes in the manufacture of a

medicament for treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molecule, wherein the cytotoxic T lymphocytes recognise at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell and they ~~are not derived from the patient with a disease.~~

20 ~~22~~. A method of making a clonal population of cytotoxic T lymphocytes (CTL) reactive against a selected molecule the method comprising the step of (a) co-culturing a sample containing CTL or a precursor, thereof derived from a healthy individual with a stimulator cell which expresses HLA class I (or equivalent) molecules on its surface and that presents at least a part of the selected molecule in a large proportion of occupied said HLA class I (or equivalent) molecules present on the surface of said stimulator cell and (b) selecting a CTL clone reactive against said selected molecule when at least a part of said molecule is presented by an HLA class I (or equivalent) molecule on the surface of a cell,

~~23. A method according to Claim 22~~ wherein the healthy individual does not carry the HLA class I (or equivalent) molecule type which, on the stimulator cell, presents at least a part of the selected molecule.

21 ~~24~~. A method according to Claim ~~22 or 23~~ 20 wherein said sample containing CTL or a precursor thereof is PBMC.

22 ~~25~~. A method according to ~~any one of~~ Claims ~~22 to 24~~ 20 wherein said molecule is a polypeptide.

23 ~~26~~. A method according to any one of Claims ~~22 to 25~~ 20 to 22 wherein said selected molecule is an abnormal molecule associated with a diseased cell, or a molecule associated with a diseased cell wherein an abnormally elevated amount of said molecule is present in said diseased cell.

24 ~~27~~. A method according to Claim ~~26~~ 23 wherein the said selected molecule is a mutant polypeptide associated with a diseased cell or a polypeptide present at a higher level in said diseased cell compound to a non-diseased cell.

25 ~~28~~. A method according to Claim ~~26~~ 23 or ~~27~~ 24 wherein said diseased cell is any one of a cancer cell, a virus-infected cell, a bacterium infected cell and a cell expressing an abnormally elevated amount of a hormone.

26 ~~29~~. A method according to any one of Claims ~~22~~ 20 to ~~28~~ 25 wherein the healthy individual is a human.

27 ~~30~~. A method according to Claim ~~29~~ 26 wherein the said selected molecule is any one of cyclin D1, cyclin E, mdm 2, EGF-R, erb-B2, erb-B3, FGF-R, insulin-like growth factor receptor, Met, myc, p53, BCL-2, ie mutant Ras, mutant p53 a polypeptide associated with the BCR/ABL translocation in CML and ALL; mutant CSF-1 receptor, mutant APC, mutant RET, mutant EGFR, a polypeptide associated with PML/RARA translocation in PML, a polypeptide associated with E2A-PBX1 translocation in pre B leukaemias and in childhood

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acute leukaemias, human papilloma virus proteins, Epstein-Barr virus proteins, HTLV-1 proteins, hepatitis B or C virus proteins, herpes-like virus proteins and HIV encoded proteins.

A method according to any one of Claims 22 to 30 further comprising determining the HLA class I (or equivalent) type of the healthy individual.

A method according to Claim 31 wherein said HLA class I (or equivalent) type is determined by DNA analysis.

A method according to any one of Claims 20 to 32 wherein said stimulator cell has a type of HLA class I (or equivalent) molecule on its surface which HLA class I (or equivalent) molecule type is not present in the healthy individual.

A method according to any one of Claims 22 to 33 wherein said stimulator cell is a cell which is substantially incapable of loading said HLA class I (or equivalent) molecule with at least a part of said selected molecule.

A method according to Claim 34 wherein said cell is a mammalian cell defective in the expression of a peptide transporter.

A method according to Claim 35 wherein the mammalian cell lacks or has a reduced level of the TAP peptide transporter.

A method according to Claim 34 wherein said cell is an insect cell.

A method according to Claim 37 wherein said cell is a *Drosophila*

cell.

36 ~~39~~. A method according to any one of Claims ~~22~~ 20 to ~~38~~ 35 wherein the stimulator cell is a host cell transfected with a nucleic acid molecule capable of expressing said HLA class I (or equivalent) molecule.

~~37~~ ~~40~~. A method according to Claim ~~39~~ 36 wherein said host cell before transfection expresses substantially no HLA class I (or equivalent) molecules.

38 ~~41~~. A method according to any one of Claims ~~22~~ 20 to ~~40~~ 37 wherein said stimulator cell expresses a molecule important for T cell costimulation.

39 ~~42~~. A method according to Claim ~~41~~ 38 wherein the molecule important for T cell costimulation is any of B7.1, B7.2, ICAM-1 and LFA3.

40 ~~43~~. A method according to any one of Claims ~~22~~ 20 to ~~42~~ 39 wherein substantially all said HLA class I (or equivalent) molecules expressed on the surface of said stimulator cell are of the same type.

41 ~~44~~. A clonal population of cytotoxic T lymphocytes reactive against a selected molecule obtainable by the method of any one of Claims ~~22~~ 20 to ~~43~~ 40.

~~45. A clonal population of cytotoxic T lymphocytes reactive against a selected molecule wherein the said CTL has a high avidity for a cell presenting said selected molecule in a HLA class I (or~~

~~equivalent) molecule.~~

42 ~~46~~. A clonal population of cytotoxic T lymphocytes according to Claim 41 ~~44 or 45~~ for use in medicine.

43 ~~47~~. A pharmaceutical composition comprising a clonal population of cytotoxic T lymphocytes reactive against a selected molecule according to Claim 41 ~~44 or 45~~ and a pharmaceutically acceptable carrier.

44 ~~48~~. Use of a clonal population of cytotoxic T lymphocytes derived from a healthy individual and reactive against a selected abnormal molecule derived from a diseased cell from a patient with a disease, or a selected molecule derived from a diseased cell from a patient with a disease wherein an abnormally elevated amount of said molecule is present in said diseased cell, in the manufacture of a medicament for treating a patient with the disease wherein said healthy individual has a different HLA type to said patient with respect to the presentation of said selected molecule

20 45 ~~49~~. A library of CTL clones, said library comprising a plurality of CTL clones derived from individuals and each said CTL clone is restricted by a different HLA class I allele and recognises a molecule associated with a selected disease.

25 46 ~~50~~. A therapeutic system comprising (a) means to determine the HLA class I (or equivalent) type of a patient to be treated and (b) a library of CTL clones as defined in Claim ~~49~~ 45.

47 ~~51~~. A method of making a cytotoxic T lymphocyte (CTL) suitable for treating a patient, the method comprising making a clonal

population of CTL by the method of any one of Claims 22 to 43; preparing a genetic construct capable of expressing the T-cell receptor (TCR) of the said clonal population of CTL, or a functionally equivalent molecule; and introducing said genetic construct into a CTL or precursor thereof which CTL or precursor is derived from said patient.

48 52. A cytotoxic T lymphocyte suitable for treating a patient obtainable by the method of Claim 51.

49 53. A method of treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and which cells are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molecule, the method comprising administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL) which recognise at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell wherein the CTL is a CTL according to Claim 52.

50 54. Use of cytotoxic T lymphocytes in the manufacture of a medicament for treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molecule, wherein the cytotoxic T lymphocytes recognise at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell and wherein the CTL

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is a CTL according to Claim 52.

~~55. Any novel method of treatment using cytotoxic T lymphocytes as herein disclosed.~~

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